Rejection under 35 U.S.C. § 112, first paragraph (written description)

In section 5 of the Action, claims 104 and 107-112 are rejected under 35 U.S.C. § 112 first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner alleges that certain subject matter of the instant claims constitutes new matter.

Applicants respectfully traverse this rejection. The present claims are directed to a WT1 immunogenic portion consisting of SEQ ID NO:2, or a variant of SEQ ID NO:2 containing between 1 and 3 amino acid substitutions, wherein the ability of the variant to react with WT1-specific T-cells is not substantially diminished. Support for each element of the currently pending claims can be found throughout the applicants' specification as originally filed. Extensive discussion of variants of the present invention can be found, for example, from page 12, line 28 to page 14, line 8, and elsewhere. This includes a description of variants containing between 1 and 3 amino acid substitutions, includes a description that variants of the invention retain reactivity with antigen specific T-cell lines or clones, and includes, as further addressed below, guidance as to the meaning of the phrase "not substantially diminished." Applicants thus submit that the presently pending claims are indeed fully supported by the specification as originally filed and respectfully request reconsideration and withdrawal of the Examiner's rejection.

Regarding "immunogenic compositions," the Examiner asserts that such language is not supported by the specification as filed. Applicants respectfully disagree and submit that the skilled artisan, in view of the specification as filed, and further in view of the level of knowledge within this art, would recognize that the applicants were indeed in clear possession of immunogenic WT1 compositions. Nevertheless, in an effort to expedite prosecution of this application, applicants have amended the claims, without prejudice, by removing the phrase "immunogenic composition" in favor of the more generic term "composition." Reconsideration of this rejection is thus respectfully requested.

In section 6 of the Action, the Examiner rejects claims 66-68, 70, 71, and 73 under 35 U.S.C. § 112 first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully point out that these claims are not currently under consideration and assume, based on the context of the Examiner's rejection regarding "variant" language, that this rejection was intended instead to apply to independent claims 104 and 110, and claims dependent therefrom.

As for the "variant" language of independent claims 104 and 110, these claims have been amended to specify that the WT1 compositions consist of the p117-139 immunogenic portion set forth in SEQ ID NO:2 or a variant thereof that differs from the immunogenic portion due to substitutions at between 1 and 3 amino acid positions within the immunogenic portion, such that the ability of the variant to react with antigen-specific T-cell lines or clones is not substantially diminished. These amendments are fully supported by the specification as filed, as addressed above. As described in the applicants' specification, p117-139 represents a WT1 peptide with motifs appropriate for binding to class I and class II MHC, and was identified using TSITES and BIMAS HLA peptide binding prediction analyses (e.g., page 44, lines 12-16, and Table I). Immunization with p117-139 peptide was demonstrated by the applicants to elicit a proliferative T cell response in vivo (e.g., page 45, lines 24-26; also Figures 5A-5C). Moreover, the WT1-specific T cells stimulated in vivo were demonstrated, using a chromium release assay, to be capable of killing WT1 positive tumor cells, whereas no killing of WT1 negative tumor cells was observed (e.g., page 97, lines 7-17). Thus, the applicants have identified T cells specific for SEQ ID NO: 2 that are capable of recognizing and lysing tumor cells expressing WT1.

Importantly, these WT1-specific T-cells identified by the applicants can be routinely isolated and used in the identification of the immunogenic variants of SEQ ID NO 2, such as those presently claimed. For example, a series of variants of SEQ ID NO:2, having up to 3 amino acid substitutions, can be synthesized and compared with SEQ ID NO:2 in their ability

to stimulate proliferation of the WT1-specific T-cells. As disclosed by the applicants, at page 13, lines 3-9:

> (T)he ability of a variant to react with antigen-specific antisera and/or T-cell lines or clones may be enhanced or unchanged, relative to the native polypeptide, or may be diminished by less than 50%, and preferably less than 20%, relative to the native polypeptide. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antisera and/or T-cells as described herein.

Applicants submit that the skilled artisan would readily understand, in light of the applicants' disclosure, the single identifying characteristic common to the claimed variants, i.e., their ability to stimulate T cells specific for SEQ ID NO:2, and would further appreciate the routine nature of the techniques used in their identification. Thus, in view of the applicants specification, and the routine and art recognized approaches for the identification and evaluation of variants that are reactive with antigen-specific T-cells, the person of ordinary skill in the art would recognize that the applicants were indeed in possession of the presently claimed invention as of the filing date of the captioned application. Reconsideration of the Examiner's rejection under 35 USC 112, first paragraph is thus respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

In section 7 of the Action, claim 107 is rejected as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleges that the specification does not disclose how to use the claimed pharmaceutical compositions for the treatment of cancer *in vivo* in humans and that undue experimentation would thus be required of one skilled in the art to practice the invention.

Applicants respectfully submit that claim 107 is directed to pharmaceutical compositions, and does not claim the treatment of cancer. Consequently, establishing therapeutic efficacy is not required on the part of the applicants in order to satisfy enablement under 35 U.S.C. 112, first paragraph, as suggested by the Examiner. In the interest of expediting prosecution of this case, however, applicants have amended claim 107 at this time, without

prejudice, by replacing the phrase "pharmaceutical composition" with the generic term "composition." Reconsideration of the Examiner's rejection is respectfully requested.

Rejections under 35 U.S.C. § 102(b)

In section 9, the Examiner rejects claims 104 and 107 as being anticipated by Herlyn, *et al.* The Examiner alleges that Herlyn et al. teach a peptide comprising SEQ ID NO:2 wherein said peptide is immunogenic (e.g. it induces antibodies). While not acquiescing to the Examiner's rejection, the presently amended claims are now directed to compositions comprising an immunogenic portion of a native WT1, wherein the immunogenic portion consists of SEQ ID NO:2. Applicants submit that the presently claimed invention is indeed novel over Herlyn et al., on the basis that this reference fails to teach an immunogenic WT1 peptide consisting of SEQ ID NO:2, much less that the peptide is effective for eliciting antibody, T helper and/or CTL responses. Applicants submit that this ground for rejection has thus been obviated and respectfully request its withdrawal.

Rejections under 35 U.S.C. § 102(a) or 102(e)

In section 10 of the Action, claims 104, 107, and 108 are rejected as being anticipated by Call et al. Call et al. allegedly teach an immunogenic peptide comprising SEQ ID NO:2 wherein said peptide is in a pharmaceutically acceptable excipient.

Applicants note that the pending claims have been amended to specify that the claimed WT1 immunogenic portion consists of SEQ ID NO:2. Call et al. describe the use of WT1 and two different WT1 peptides to generate poly and monoclonal antibodies in mice. Neither of the peptides used by Call et al., however, consist of the sequence set forth in SEQ ID NO:2, nor does Call et al. teach or suggest that a WT1 peptide consisting of SEQ ID NO:2 would be capable of effectively eliciting an immune response. Thus, Call et al. does not anticipate the presently claimed subject matter. Applicants submit that this ground for rejection has been obviated and respectfully request its withdrawal.

Rejections under 35 U.S.C. § 103(a)

Claims 104 and 107-112 are rejected as allegedly being obvious over Herlyn et al. or Call et al., in view of Jager et al. Call et al. and Herlyn et al. are discussed above. Jager et al. describes the use of GM-CSF as an adjuvant.

Applicants again note that the pending claims have been amended to specify that the claimed WT1 immunogenic portion consists of SEQ ID NO:2. Applicants' arguments to the Examiner's position regarding Call et al. and Herlyn et al. are equally applicable in the context of this rejection under 35 U.S.C. 103(a). As set forth above, Herlyn et al. and Call et al. fail to teach the specific WT1 immunogenic portions presently claimed by the applicants. Likewise, Jager et al. fails to teach the specific WT1 immunogenic portions presently claimed. In view of this, applicants respectfully submit that the cited references, taken either alone or in combination, cannot reasonably render obvious the presently claimed WT1 immunogenic portion consisting of SEQ ID NO:2, when the cited references offer no teaching or suggestion as to the existence and/or the identity of the now claimed immunogenic portion. Applicants thus respectfully request reconsideration and withdrawal of this rejection by the Examiner.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

All of the claims remaining in the application are now submitted to be allowable. The Examiner is encouraged to contact the undersigned with any questions, comments and/or suggestions pertaining to this communication.

Respectfully submitted,
Seed Intellectual Property Law Group PLLC

Jeffrey E. Hundley, Ph.D.
Registration No. 42,676

JEH:sds
Enclosures:
Postcard
Check
Petition for an Extension of Time

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900/Fax: (206) 682-6031
D:\NrPortbl\iManage\SHARONS\211731_1.DOC

09/164,223

210121.465

Version with Markings to Show Changes Made

In the Specification:

Any of a variety of non-specific immune response enhancers, such as adjuvants, may be employed in the vaccines of this invention. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable non-specific immune response enhancers include alum-based adjuvants (*e.g.*, Alhydrogel, Rehydragel, aluminum phosphate, Algammulin, aluminum hydroxide); oil based adjuvants (Freund's adjuvant (FA), Specol, RIBI, TiterMax, Montanide ISA50 or Seppic MONTANIDE ISA 720; cytokines (*e.g.*, GM-CSF or Fl[a]t3-ligand); microspheres; nonionic block copolymer-based adjuvants; dimethyl dioctadecyl ammoniumbromide (DDA) based adjuvants AS-1, AS-2 (Smith Kline Beecham); Ribi Adjuvant system based adjuvants; QS21 (Aquila); saponin based adjuvants (crude saponin, the saponin Quil A); muramyl dipeptide (MDP) based adjuvants such as SAF (Syntex adjuvant in its microfluidized form (SAF-m)); dimethyl-dioctadecyl ammonium bromide (DDA); human complement based adjuvants *m. vaccae* and derivatives; immune stimulating complex (iscom) based adjuvants; inactivated toxins; and attenuated infectious agents (such as *M. tuberculosis*).

In the Claims:

Please amend claims 104 and 107-112 as follows:

104. (Amended) A polypeptide ~~comprising~~ consisting of an immunogenic portion of native WT1, or a variant thereof that differs from the immunogenic portion due to substitutions at between 1 and 3 amino acid positions within the immunogenic portion, ~~in one or more substitutions, deletions, additions and/or insertions~~ such that the ability of the variant to

react with WT1-specific ~~antisera and/or~~ T-cell lines or clones is not substantially diminished, wherein the immunogenic portion consists of the contiguous amino acids of SEQ ID NO:2 ~~or 3~~.

107. (Amended) ~~A pharmaceutical~~ composition comprising ~~a polypeptide~~ an immunogenic portion of native WT1 ~~according to claim 104~~, wherein the immunogenic portion consists of the contiguous amino acids of SEQ ID NO:2 in combination with a pharmaceutically acceptable carrier or excipient.

108. (Amended) ~~An immunogenic~~ composition comprising ~~a polypeptide~~ an immunogenic portion of native WT1, wherein the immunogenic portion consists of the contiguous amino acids of SEQ ID NO:2 ~~according to claim 104~~, in combination with a non-specific immune response enhancer.

109. (Amended) A ~~immunogenic~~ composition according to claim 108, wherein the immune response enhancer is an adjuvant.

110. (Amended) A ~~immunogenic~~ composition comprising:

(a) a WT1 polypeptide ~~, wherein the polypeptide comprises~~ consisting of an immunogenic portion of a native WT1 or a variant thereof that differs from the immunogenic portion due to substitutions at between 1 and 3 amino acid positions within the immunogenic portion, ~~in one or more substitutions, deletions, additions and/or insertions~~ such that the ability of the variant to react with antigen-specific T cell lines or clones is not substantially diminished; and

(b) a non-specific immune response enhancer that preferentially enhances a T cell response in a patient;

wherein said ~~WT1 polypeptide~~immunogenic portion ~~comprises~~ consists of the contiguous amino acids of SEQ ID NO:2.

111. (Amended) A ~~immunogenic~~ composition according to claim 110, wherein the immune response enhancer is selected from the group consisting of Montanide

ISA50, Seppic Montanide ISA 720, a cytokine, a microsphere, dimethyl dioctadecyl ammoniumbromide (DDA) based adjuvants, AS-1, AS-2, Ribi Adjuvant system based adjuvant, QS21, saponin based adjuvants, Syntex adjuvant in its microfluidized form, MV, ddMV, immune stimulating complex (iscom) based adjuvants, and inactivated toxins.

112. (*Amended*) The ~~immunogenic~~ composition of claim 111, wherein said cytokine is selected from the group consisting of GM-CSF and ~~Flat3~~Flt3-ligand.